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Health-related Quality of Life in Women With Recurrent Ovarian Cancer Receiving Paclitaxel Plus Trebananib or Placebo (TRINOVA-1)

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Abstract

Background: To evaluate the influence of treatment on health-related quality of life (HRQoL) in 919 women with recurrent ovarian cancer enrolled in the TRINOVA-1 study, a randomized, placebo-controlled phase 3 study that demonstrated that trebananib 15 mg/kg QW plus weekly paclitaxel significantly improved PFS compared with placebo plus weekly paclitaxel (7.2 versus 5.4 months; hazard ratio, 0.66; 95% CI, 0.57–0.77; *P*<0.001).

Patients and Methods: HRQoL was assessed with the Functional Assessment of Cancer Therapy–Ovary (FACT-O; comprising FACT-G and the ovarian cancer–specific subscale [OCS]) and EuroQOL EQ-5D instruments before treatment on day 1 of weeks 1, 5, 9, 13, 17, and every 8 weeks thereafter and at the safety follow-up visit. A pattern-mixture model was used to evaluate influence of patient dropout on FACT-O and OCS scores over time.

Results: 834 of 919 randomized patients (91%) had a baseline and ≥1 post-baseline HRQoL assessment. At baseline, scores for all instruments were similar for both arms. At 25 weeks mean ± SD changes from baseline were negligible, with mean ± SD changes typically <1 unit from baseline: −2.4±16.6 in the trebananib arm and −1.6±15.2 in the placebo arm for FACT-O, −0.71±5.5 in the trebananib arm and −0.86±4.9 in the placebo arm for OCS, and −0.02±0.22 in the trebananib arm and 0.02±0.19 in the placebo arm for EQ-5D. Distribution of scores was similar between treatment arms at baseline and over the course of the study. In pattern-mixture models, there was no evidence that patient dropout affected differences in mean FACT-O or OCS scores. Edema had limited effect on either FACT-O or OCS scores in patients with grade ≥2 edema or those with grade 1 or no edema.

Conclusions: Our results demonstrate that the improvement in PFS among patients in the trebananib arm in the TRINOVA-1 study was achieved without compromising HRQoL.

Abstract word count: 300 (limit, 300)

Key words: Trebananib, Recurrent Ovarian Cancer, Health-related Quality of Life, Edema

Clinical trial registration: ClinicalTrials.gov identifier, NCT01204749

Key Message: "Results from the TRINOVA-1 study of trebananib plus weekly paclitaxel versus placebo plus paclitaxel in women with recurrent ovarian cancer demonstrate that the improvement in PFS among patients in the trebananib arm was achieved without compromising HRQoL."

Introduction

Angiogenesis is critical for solid tumor growth and metastasis [1]. Angiogenesis is regulated by a number of distinct pathways including the vascular endothelial growth factor (VEGF) pathway and the angiopoietin axis [2]. In the angiopoietin axis, the ligands angiopoietin-1 and angiopoietin-2 interact with the Tie2 receptor, thereby initiating the angiogenic switch and promoting neovascularization [2]. Trebananib is an investigational peptide-Fc fusion protein that neutralizes the interaction between angiopoietin-1 and angiopoietin-2 and the Tie2 receptor, thereby suppressing angiogenesis [3].

TRINOVA-1 [4] was a randomized, double-blind, placebo-controlled phase 3 study evaluating weekly trebananib plus paclitaxel in 919 women with recurrent, platinum-resistant or partially platinum-sensitive ovarian cancer. Compared with paclitaxel plus placebo, trebananib plus paclitaxel significantly improved the primary endpoint of progression-free survival (PFS; 7.2 versus 5.4 months; hazard ratio, 0.66; 95% CI, 0.57–0.77; $P<0.001$) and significantly improved the objective response rate (38% versus 30%; $P=0.0071$) [4]. Most AEs were consistent with those anticipated for patients with recurrent ovarian cancer receiving weekly paclitaxel [5]. Edema was the most frequent AE with a ≥10% difference in the treatment arm. Most edema events were of grade 1/2; grade 3 edema led to discontinuation of treatment in 8% of patients in the trebananib arm versus 1% in the placebo arm [4].

When evaluating the benefit of an investigational treatment regimen, it is important to consider whether improvements in outcomes occur at the expense of patients' health-related quality of life (HRQoL). This is particularly relevant for patients with recurrent ovarian cancer who undergo radical surgery and multiple rounds of cytotoxic chemotherapy during the course of their illness [6]. HRQoL can be significantly

disrupted, and there is debate regarding the appropriate balance between benefits of treatment and toxicity [7]. In the TRINOVA-1 study, the PFS benefit and objective tumor response associated with the combination of trebananib plus paclitaxel must be weighed against the risk of toxicity and its potential to compromise HRQoL. To examine whether addition of trebananib to paclitaxel affected HRQoL in TRINOVA-1, the objectives of the study included estimation of the effects of trebananib on patient-reported symptoms specific to ovarian cancer using the Functional Assessment of Cancer Therapy–Ovary (FACT-O) questionnaire and its effects on patient-reported overall health status using the EuroQOL EQ-5D questionnaire. Because edema was more frequent in patients receiving trebananib, we also evaluated whether this AE affected HRQoL.

Methods

Eligibility

Complete eligibility criteria have been described previously [4]. Briefly, women were eligible if they were ≥18 years, had radiographic evidence of disease progression <12 months after receiving platinum-based chemotherapy (ie, platinum-free interval [PFI] ≤12 months), and had evaluable disease per RECIST version 1.1 with modifications [8]. Patients were excluded if they had received >3 previous lines of chemotherapy; platinum-refractory disease; or borderline, mucinous, or clear-cell histology. Patients provided written informed consent; the study protocol and procedures received approval from institutional ethics committees.

Study Design and Treatment

Patients were randomized 1:1 to receive intravenous trebananib 15 mg/kg once weekly (QW) plus paclitaxel (trebananib arm) or intravenous placebo QW plus paclitaxel (placebo arm). Paclitaxel infusions followed a 4-week treatment cycle and were administered during weeks 1, 2, and 3. Randomization was stratified by PFI (PFI >0 and ≤6 months/PFI >6 and ≤12 months), presence/absence of measurable disease, and geographic region (North America, Western Europe, or Australia/rest of world). Treatment was discontinued if patients had disease progression per modified RECIST [8], experienced unacceptable toxicity, or withdrew consent.

PRO and HRQoL Assessments

To evaluate HRQoL, patients completed the FACT-O and the EuroQoL EQ-5D. FACT-O is a 39-item self-report questionnaire consisting of the Functional Assessment of Cancer Therapy–General (FACT-G) and ovarian cancer–specific (OCS) subscales. The 27-item FACT-G assesses four domains of well-being: physical, social, emotional, and functional aspects [9]. The OCS consists of 12 items evaluating symptoms specific to ovarian cancer. For the FACT-G and OCS subscales, respondents rated each item on a 5-point Likert scale from 0 (not at all) to 4 (very much) based on their experience during the past 7 days. The OCS yields a combined summary score ranging between 0 and 48, with higher scores indicative of better HRQoL [9, 10].

Overall health status was assessed with the EQ-5D. Respondents completed the EQ-5D by indicating their health state in the areas of mobility, self-care, usual activities, pain/discomfort, and anxiety/depression [11]. Ratings in each domain of the EQ-5D were combined to produce a weighted index score, with higher ratings indicating

improved overall health status. Additionally, respondents rated overall health on the EQ-5D visual analog scale (VAS) from 0 (worst imaginable) to 100 (best imaginable).

Questionnaires were administered before patients received treatment or completed clinical assessments on day 1 of weeks 1, 5, 9, 13, 17; every 8 weeks up to 2 years, then every 6±1 months thereafter; and at the safety follow-up visit. The EQ-5D was always administered after the FACT-O (ie, FACT-G and OCS). If an unscheduled radiologic assessment coincided with a scheduled HRQoL assessment, completion of the HRQoL assessment was postponed until the next visit to ensure the outcome of radiologic assessment did not influence HRQoL assessment. HRQoL questionnaires were only administered to women able to complete them independently and for whom appropriate translations were available (if necessary). HRQoL assessments ceased after disease progression.

Statistical Analysis

Evaluation of HRQoL and ovarian cancer-related symptoms using FACT-O and evaluation of overall health status using EQ-5D were prespecified secondary study endpoints. Patients were included in analyses (PRO-evaluable set) if they had a baseline and ≥1 post-baseline HRQoL assessment before disease progression per modified RECIST [8]. As previously described [4], a pattern-mixture model [12] was used to evaluate whether there were changes in FACT-O and OCS scores over time, adjusting for dropout (any-cause). This model stratifies patients by their last completed PRO assessment, thereby accounting for data missing not-at-random between dropout patterns.

Results

Patient Characteristics

Overall, 919 patients (trebananib arm, n=461; placebo arm, n=458) were enrolled between November 10, 2010, and November 19, 2012. The PRO-evaluable set included 834 (91%) patients. Baseline demographic/clinical characteristics were similar between treatment arms and between the intent-to-treat population and PRO subset (**Table 1**). Most patients (57%) had a GOG performance score of 0 (fully active, unrestricted activities of daily living) and 24% had history of ascites. Overall, 39% of patients had received one previous line of therapy, 38% received two, and 23% received three.

PRO and HRQoL

Completion rates were high for all questionnaires at baseline and among patients who had not progressed at later time points (**Figure 1**). Completion rates were consistently high throughout the study.

At baseline, patients in the trebananib and placebo arms reported similar mean±SD scores for the FACT-O (trebananib 106.3±20.6; placebo, 106.6±20.7), OCS (30.3±5.9; 30.2±6.1), and EQ-5D (0.75±0.20; 0.74±0.24). At 25 weeks (which approximates median PFS time in the study), mean±SD changes from baseline were negligible, with changes typically <1 unit from baseline: −2.4±16.6 in the trebananib arm and −1.6±15.2 in the placebo arm for FACT-O, −0.71±5.5 in the trebananib arm and

−0.86±4.9 in the placebo arm for OCS, and −0.02±0.22 in the trebananib arm and 0.02±0.19 in the placebo arm for EQ-5D (**Figure 2**). Similar patterns were seen for the EQ-5D VAS (**Supplementary Figure 1**). Subscale scores of the FACT-O provided little evidence of differences in patients' assessment of physical, social, emotional, and functional well-being during the first 25 weeks of the study (data not shown).

Supporting the descriptive utility of the mean/median population scores, we also evaluated the distribution of scores across patient groups. Cumulative frequency plots for FACT-O, OCS, and EQ-5D showed that the distribution of scores was similar between arms at baseline and the distribution remained similar between arms over the course of the study (**Figure 3**).

Dropout patterns had little effect on treatment differences in FACT-O or OCS mean summary scores. In pattern-mixture models [4], patients were classified as either early dropouts (last visit at or before 25 weeks) or late dropouts (last visit after 25 weeks). For FACT-O, least squares adjusted mean for the treatment difference was −2.44 for early dropouts (n=614) and −1.65 for late dropouts (n=188). For OCS, it was −0.68 for early dropouts (n=623) and 0.17 for late dropouts (n=192).

Associations Between Edema and HRQoL

Incidence of edema was greater in the trebananib arm than in the placebo arm (any grade, 64% vs 28%; grade ≥3, 10% vs 1%). In exploratory analyses, we examined the influence of treatment-emergent edema on FACT-O and OCS summary scores. Patients with grade ≥2 edema exhibited slightly larger decreases from baseline in FACT-O and OCS scores compared with patients with grade 1 or no edema, but the scores were variable with no consistent pattern of compromised HRQoL among patients in the trebananib arm with grade ≥2 edema (**Figure 4**). Overall, the data was not suggestive of

a differential influence of edema on FACT-O and OCS summary scores between treatment arms.

Discussion

The TRINOVA-1 study included a rigorous and systematic assessment of HRQoL. Overall, these analyses demonstrated that the improvement in PFS and objective response rate among patients in the trebananib group [4] was achieved without compromising HRQoL. The lack of influence of trebananib plus paclitaxel on HRQoL is an important finding because, in the absence of an unequivocal overall survival advantage (potentially due to long post-progression survival and the multiple lines of subsequent anticancer therapy administered), the objectives of treatment are to delay disease progression while minimizing potential negative effects of treatment-related toxicity.

Our results represent one of the largest studies of HRQoL in patients with recurrent ovarian cancer receiving weekly paclitaxel. Questionnaire completion rates were robust and consistent over time. Distribution of patient scores was also similar over time, indicating that means were appropriate descriptors of aggregate out HRQoL across the study population. We observed only small differences in outcomes across questionnaires that evaluated physical, social, emotional, and functional aspects of well-being (FACT-O), symptoms specific to ovarian cancer (OCS), and global health status (EQ-5D). Moreover, mean decrements in HRQoL scores from baseline appeared to be smaller than the established clinically important differences (FACT-O, six-point change [10]; EQ-5D, 0.06-point change in patients with cancer [13]). Notably, the similarity in distribution of scores between the trebananib and placebo arms was observed

throughout the study suggesting that patients who remained in treatment did not experience reduced HRQoL as treatment continued. Given that the patients' baseline demographic characteristics suggested many had asymptomatic disease at study entry (eg, age, GOG performance status), improvements in HRQoL during treatment were not anticipated.

Exploratory analyses suggested that incidence of treatment-emergent edema (an AE that occurs more frequently among patients receiving trebananib) [14] did not meaningfully alter patients' HRQoL. Most edema events occurring while patients were on-study were mild in severity (grade 1/2), and our analyses provide additional important information by assessing the patient perspective of edema and its impact on HRQoL. Although there was a suggestion of a small decrement in HRQoL among patients with edema, the relative magnitude of the questionnaires' measurement sensitivity rather than a clinically meaningful finding.

Importantly pattern-mixture models indicated patients in the trebananib and placebo arm who dropped out of the study during the earlier phase of treatment did not differ in their ratings of HRQoL. This suggests that informative censoring due to removal of subjects from the population was unlikely to have obscured an unequal effect between treatment arms. Missing data may raise significant questions of interpretation in investigations of HRQoL. Consequently, any assumption that data are missing at random can result in underestimation of HRQoL effects. Similarly, no differences in HRQoL were observed for those patients who remained in the study longer. Together, these results suggest that the HRQoL outcomes identified in this study were not due to selective drop out of particular patient groups.

Our results provide an informative comparison with results from studies evaluating the influence of the anti-VEGF monoclonal antibody bevacizumab on HRQoL

in patients with recurrent ovarian cancer. In the open-label randomized AURELIA study, women with platinum-resistant ovarian cancer received paclitaxel, pegylated liposomal doxorubicin, or topotecan (investigator's choice) with/without bevacizumab. More patients in the bevacizumab arm (21.9%) than the chemotherapy-only arm (9.3%) rated their gastrointestinal and abdominal symptoms as improved in the bevacizumab arm after 8 weeks of treatment [15]. However, eligibility criteria for AURELIA allowed only patients with a PFI <6 months and excluded patients with a history of abdominal fistulae, gastrointestinal perforation, intra-abdominal abscess, or bowel obstruction [16]. These exclusion criteria may have resulted in enrollment of a patient population for whom improvements in gastrointestinal symptoms would be more easily achieved. It is also important to note that the primary analysis of HRQoL in AURELIA was conducted after 8 weeks of treatment with an imbalance in patient numbers favoring the bevacizumab arm (122 patients versus 84 patients); few patients were evaluable at later timepoints, particularly in the chemotherapy only arm. In the randomized placebo-controlled GOG-0218 study of first-line therapy with carboplatin/paclitaxel with/without bevacizumab the combination improved PFS but was associated with a small reduction in HRQoL scores [17], although this difference was not maintained during bevacizumab maintenance therapy [18]. In the randomized open-label ICON7 study, first-line bevacizumab plus carboplatin/paclitaxel improved PFS [19] but was associated with a small decrement in HRQoL at 54 weeks [20]. These results illustrate the influence of toxicity profile and patient characteristics on HRQoL outcomes.

Results from TRINOVA-1 suggest that the combination of trebananib plus paclitaxel compared with placebo plus paclitaxel does not compromise HRQoL in patients with platinum-resistant and partially platinum-sensitive recurrent ovarian cancer. The results of this study provide physicians with information that could guide clinical

decision making, particularly with respect to appropriate sequencing of antiangiogenic agents in women with recurrent ovarian cancer.

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Conflicts of Interest

K Fujiwara has received honoraria from Kyowa Hakko Kirin, Nippon Kayaku, Chugai, Eisai, and Roche; has been a consultant to Pfizer, Merck Sharpe & Dohme, AstraZeneca, and Eisai; has received research funding from Sanofi and Chugai; and has received travel support from Pfizer and Roche. B Monk received an honorarium from Amgen; has been a consultant for Amgen; and has received research funding from Amgen. C Lhommé has received honoraria from Amgen, Roche, PharmaMar; has been a consultant to Roche; and has received travel support from Roche and PharmaMar. R Coleman has received honoraria from NCCN; has been a consultant to Clovis Oncology, Roche/Genentech, Esperance Pharma, NCCN, and DOD-CDRMP; and has received research funding from AstraZeneca/MedImmune, Esperance, OncoMed, Array BioPharmaceuticals, Clovis Oncology, Amgen, Johnson and Johnson, and Merrimack; and has received travel support from Millennium, Merck, Amgen, AstraZeneca/Medimmune, Array Biopharma, Merrimack, and Gradalis. M Fabbro has received travel support from Roche. D Provencher has been a consultant to AstraZeneca. A Bamias has honoraria from Amgen. F Vogl and B Bach are employees and hold stock options from Amgen. I Vergote served on an advisory board at Amgen. K Zhang was an employee of Amgen Inc at the time the research was conducted. F Raspagliesi has been a consultant to Amgen, Roche, and PharmaMar; has been a speaker for Roche and PharmaMar; has received research funding from Roche, PharmaMar, and AstraZeneca; and has received travel support from Roche. A Brize, A Oaknin, I Ray-Coquard, and A De Censi have no conflicts of interest to declare.

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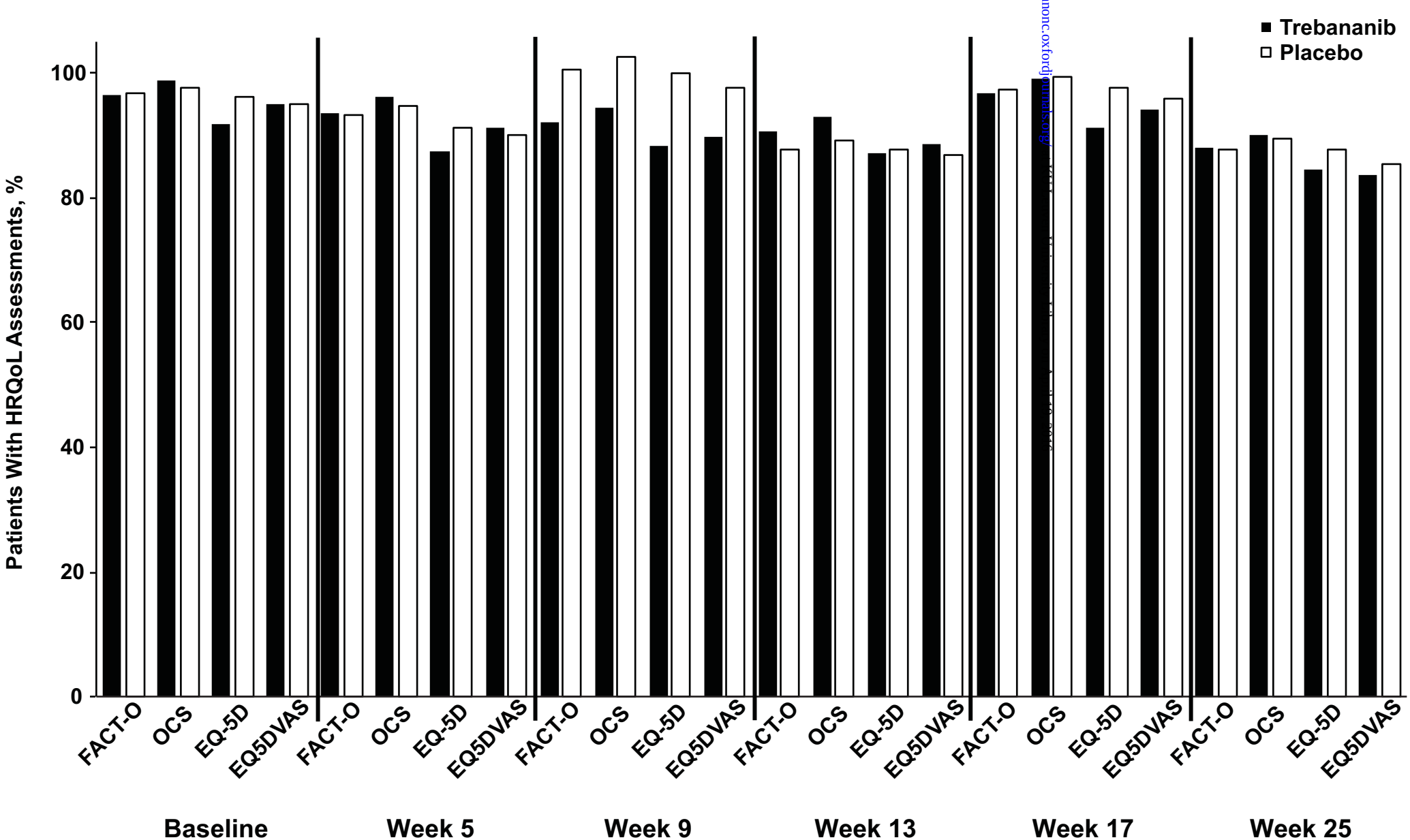
Figure Legends

Figure 1. Instrument completion rates. Data show proportion of patients with a completed questionnaire at each time point, with the denominator as the number of evaluable patients at that time point.

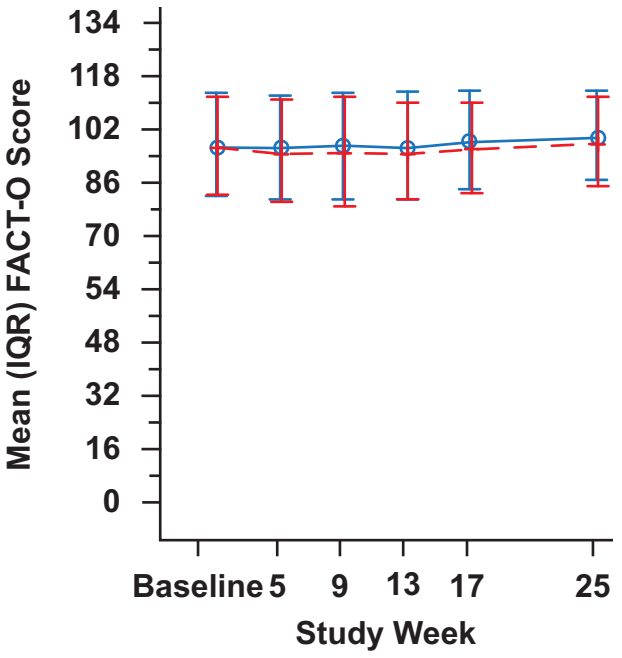
Figure 2. Mean ± interquartile range (IQR) scores for (A) FACT-O, (B) OCS, and (C) EQ-5D scores over time. FACT-O, Functional Assessment of Cancer Therapy–Ovary; OCS, ovarian cancer–specific subscale.

Figure 3. Cumulative frequency distribution plots for the (A) FACT-O, (B) OCS, and (C) EQ-5D at baseline, 9 weeks, and 25 weeks. FACT-O=Functional Assessment of Cancer Therapy–Ovary; OCS, ovarian cancer–specific subscale. The shape of the distribution of scores for each instrument was similar at each time point, indicating that paclitaxel plus trebananib and paclitaxel plus placebo were not associated with major changes in the range of values.

Figure 4. Mean ± SE (A) FACT-O and (B) OCS scores over time among patients classified as grade ≥2 edema and patients with grade 1 edema or without edema in the placebo arm (left panels) and trebananib arm (right panels) while on study. FACT-O, Functional Assessment of Cancer Therapy–Ovary; OCS, ovarian cancer–specific subscale.

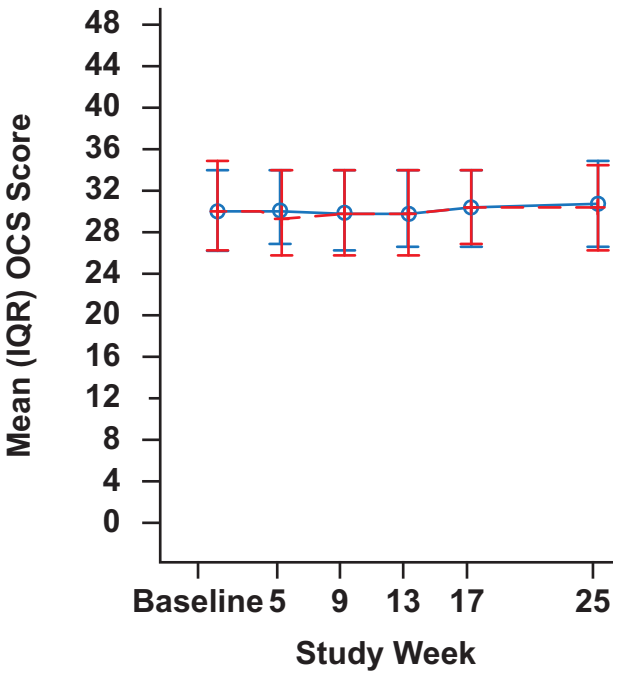

Trebananib
Placebo
Patients With HRQoL Assessments, %
0
20
40
60
80
100
FACT-O
OCS
EQ-5D
EQ5DVAS
Baseline
Week 5
Week 9
Week 13
Week 17
Week 25

A FACT-O



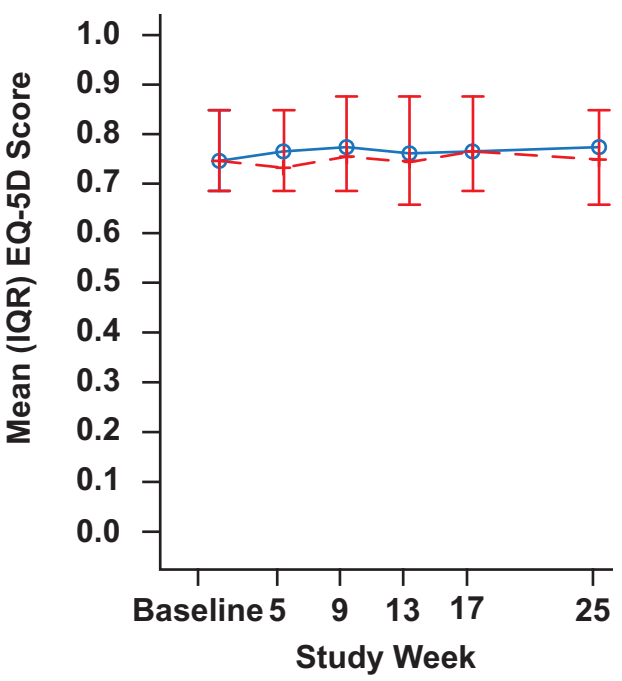
Patient Responses						
Trebananib + Paclitaxel:	392	371	325	286	255	169
Placebo + Paclitaxel:	412	393	343	263	235	146

B OCS



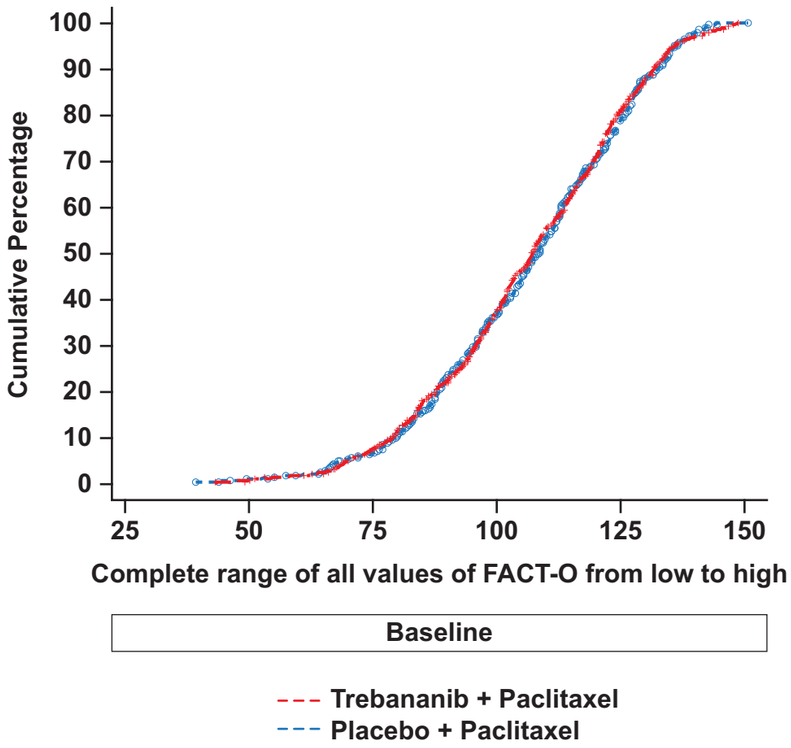
Patient Responses						
Trebananib + Paclitaxel:	401	382	333	293	260	172
Placebo + Paclitaxel:	416	399	349	268	241	149

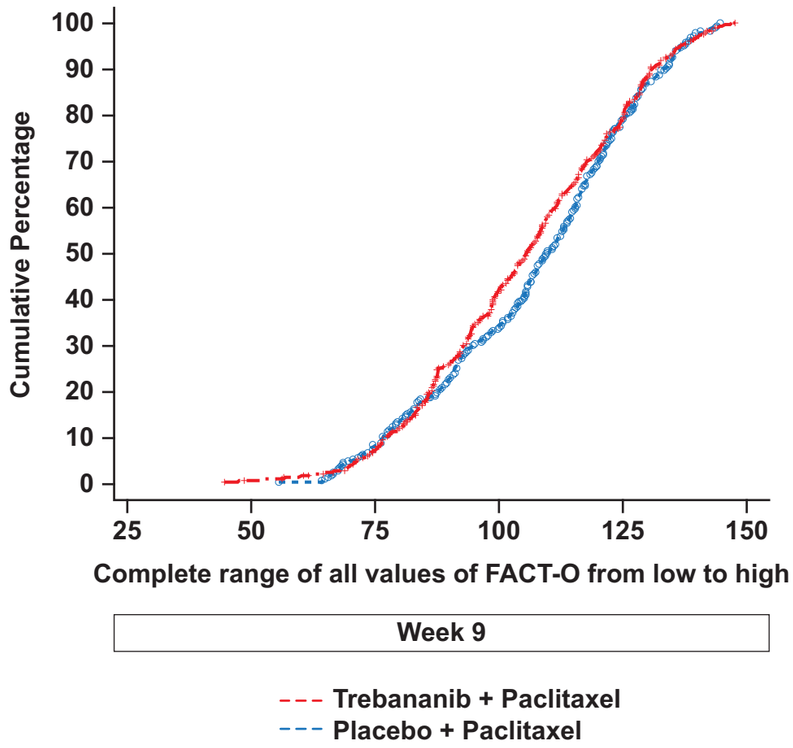
C EQ-5D

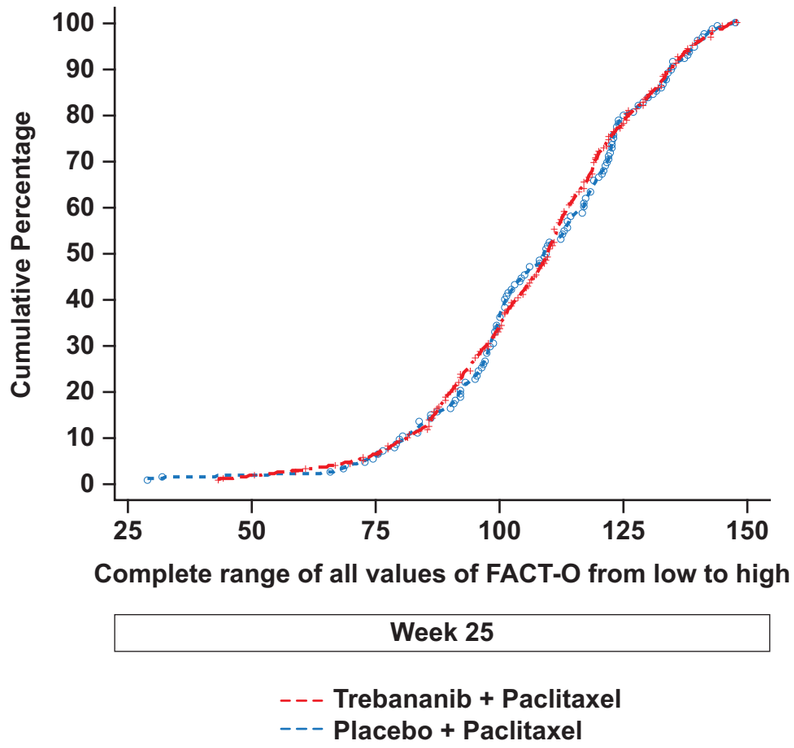


Patient Responses						
Trebananib + Paclitaxel:	372	348	308	275	241	163
Placebo + Paclitaxel:	411	385	339	262	235	146

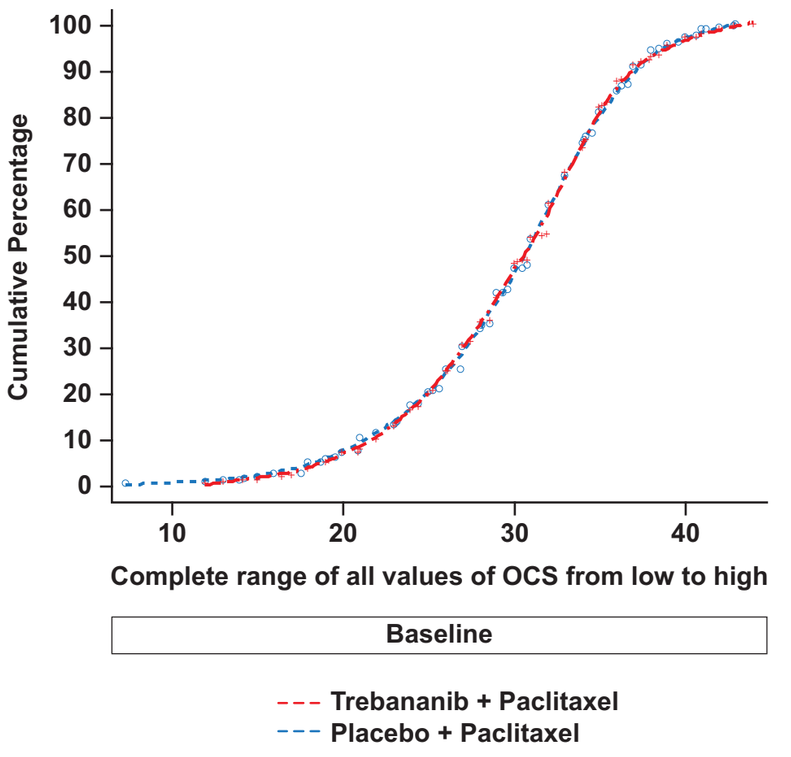
A FACT-O

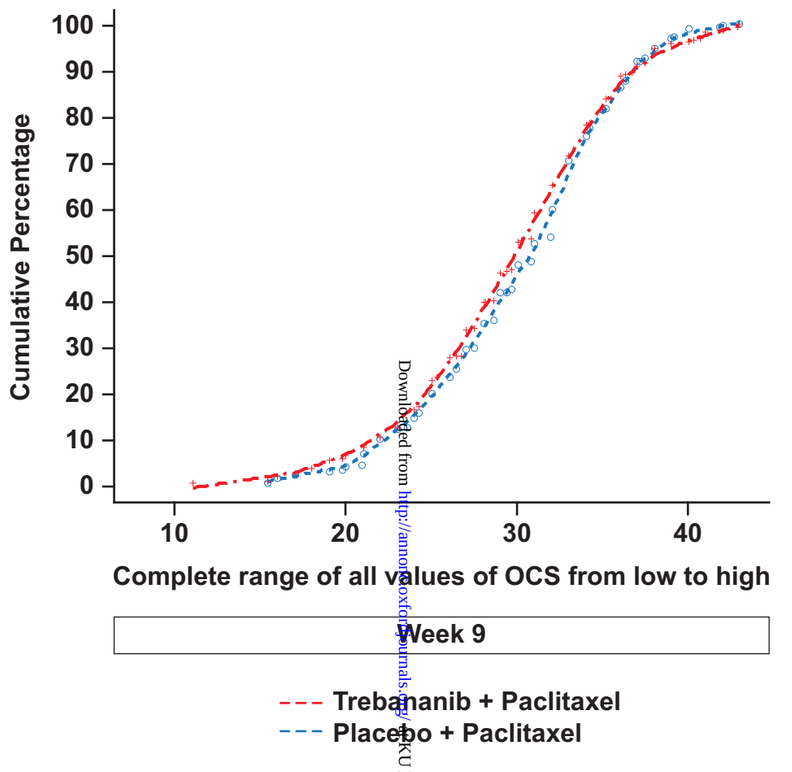


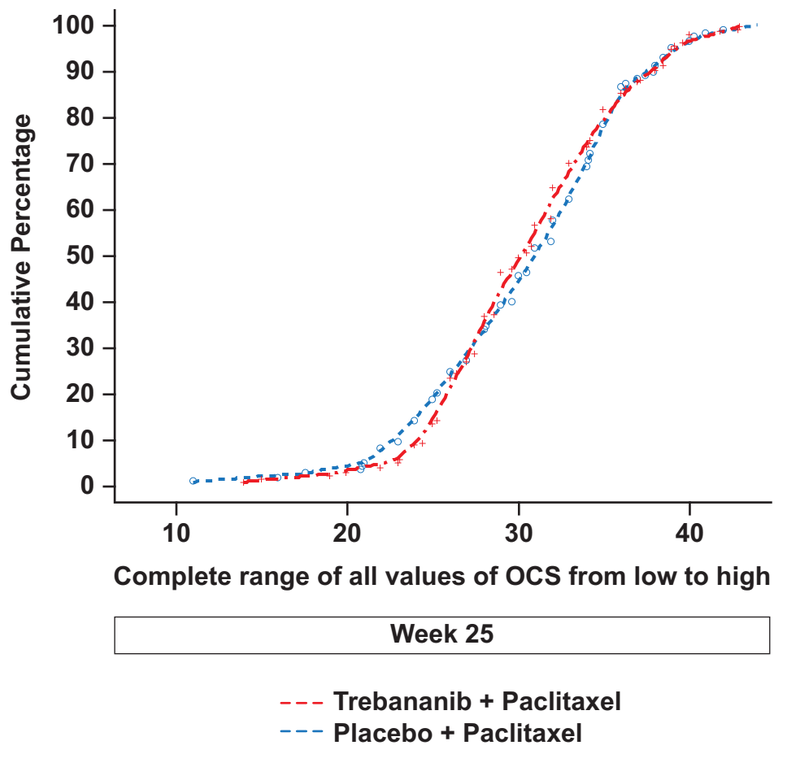




B OCS

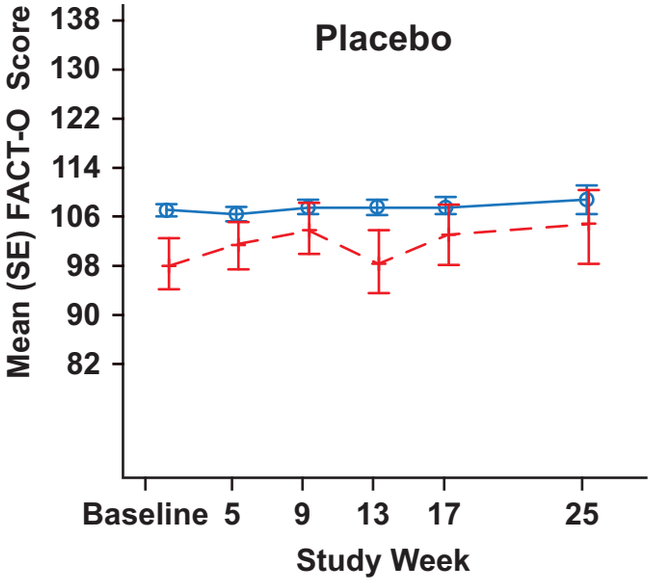




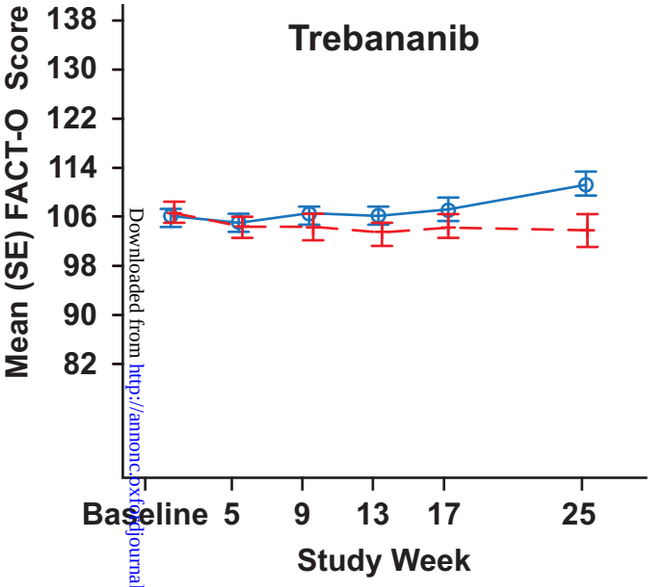


C EQ-5D

A FACT-O

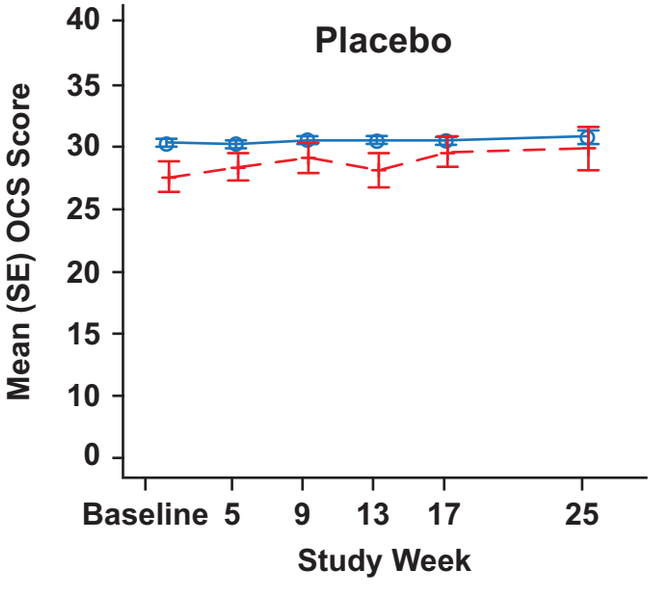


Patient Responses						
Grade ≥2 edema:	30	28	22	21	23	13
Grade 1 or without edema:	382	362	285	235	197	115

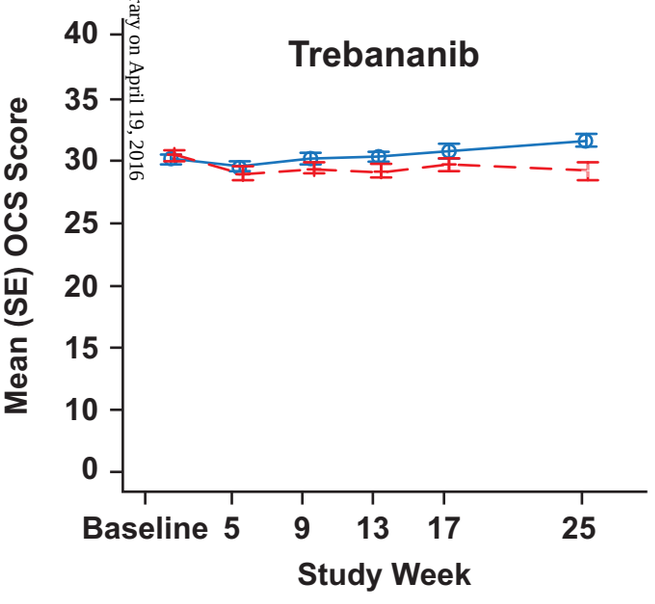


Patient Responses						
Grade ≥2 edema:	151	137	129	122	109	70
Grade 1 or without edema:	243	235	180	167	137	91

B OCS



Patient Responses						
Grade ≥2 edema:	31	29	24	22	24	14
Grade 1 or without edema:	385	367	289	239	201	117



Patient Responses						
Grade ≥2 edema:	153	139	131	125	111	72
Grade 1 or without edema:	250	244	186	172	141	93

Tables

Table 1. Baseline Demographic and Clinical Characteristics

	Intent-to-Treat Population		Patient-Reported Outcomes Subset	
	Trebananib 15 mg/kg + Paclitaxel (n = 461)	**Placebo + Paclitaxel (n = 458)**	**Trebananib 15 mg/kg + Paclitaxel (n = 408)**	**Placebo + Paclitaxel (n = 426)**
Race/ethnicity, n (%)				
White	387 (84)	363 (79)	345 (85)	341 (80)
Asian	58 (13)	82 (18)	47 (12)	74 (17)
Black	6 (1)	7 (2)	6 (1)	6 (1)
Other	10 (2)	6 (1)	10 (2)	5 (1)
Region; n (%)				
Western Europe/Australia	193 (42)	189 (41)	169 (41)	175 (41)
North America	93 (20)	91 (20)	79 (19)	83 (19)
Rest of world	175 (38)	178 (39)	160 (39)	168 (39)
Age, median (interquartile range), y	60 (51–66)	59 (50–65)	60 (51–66)	59 (50–65)
GOG performance score, n (%)				
0	259 (56)	252 (55)	239 (59)	238 (56)
1	200 (43)	205 (45)	167 (41)	187 (44)
2	2 (<1)	1 (<1)	2 (<1)	1 (<1)

	Intent-to-Treat Population		Patient-Reported Outcomes Subset	
	Trebananib 15 mg/kg + Paclitaxel (n = 461)	**Placebo + Paclitaxel (n = 458)**	**Trebananib 15 mg/kg + Paclitaxel (n = 408)**	**Placebo + Paclitaxel (n = 426)**
History of ascites at study entry, n (%)				
Yes	108 (23)	123 (27)	90 (22)	114 (27)
No	353 (77)	335 (73)	318 (78)	312 (73)
Primary tumor type, n (%)				
Ovarian cancer	423 (92)	419 (92)	373 (91)	391 (92)
Primary peritoneal carcinoma	24 (5)	24 (5)	21 (5)	21 (5)
Fallopian tube cancer	14 (3)	15 (3)	14 (3)	14 (3)
Tumor histology, n (%)				
Serous	385 (84)	388 (85)	341 (84)	360 (85)
Endometrioid	29 (6)	26 (6)	24 (6)	25 (6)
Undifferentiated	15 (3)	10 (2)	14 (3)	9 (2)
Transitional	4 (1)	2 (<1)	4 (1)	2 (<1)
Other	28 (6)	32 (7)	25 (6)	30 (7)
Histologic grade, n (%)				
Well differentiated	24 (5)	31 (7)	23 (6)	29 (7)
Moderately differentiated	69 (15)	84 (18)	65 (16)	81 (19)
Poorly differentiated	274 (59)	256 (56)	239 (59)	238 (56)
Unknown	94 (20)	87 (19)	81 (20)	78 (18)

	Intent-to-Treat Population		Patient-Reported Outcomes Subset	
	Trebananib 15 mg/kg + Paclitaxel (n = 461)	**Placebo + Paclitaxel (n = 458)**	**Trebananib 15 mg/kg + Paclitaxel (n = 408)**	**Placebo + Paclitaxel (n = 426)**
Lines of prior anticancer therapy, n (%)				
1	190 (41)	172 (38)	171 (42)	155 (36)
2	174 (38)	172 (38)	154 (38)	163 (38)
3	94 (20)	114 (25)	80 (20)	108 (23)
4	2 (<1)	0 (0)	2 (<1)	0 (0)
Not available	1 (<1)	0 (0)	1 (<1)	0 (0)
Platinum-free interval, n (%)				
≤6 months	235 (51)	245 (53)	208 (51)	227 (53)
>6 and ≤12 months	223 (48)	212 (46)	198 (49)	198 (46)
Primary platinum refractory	3 (1)	1 (<1)	2 (<1)	1 (<1)